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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,751	12/14/2005	Olivier Lambert	ON/4-33220A	3065

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
HA, JULIE	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,751	LAMBERT ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on March 21, 2007 is acknowledged. Claim 9 was cancelled and new claims 11-14 are added. Claims 1-8 and 10-14 are pending in this application.

Restriction

1. Applicant's election of Group I (claims 1-8 and 10) drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analogue and the election of peptide of formula II in the reply filed on March 21, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 10 is withdrawn from further consideration being drawn to a nonelected species. Claims 1-8 and 11-14 are examined on the merits in this office action.

Objections-Claims

2. Claims 6-8 are objected to because of the following informalities:

3. Claims 7 and 8 recite the language "Use of". "Use" claim language is improper under U.S. practice. Appropriate correction is required.

4. Claim 6 is objected to because there is a spelling error at line 2 of the claim. Glycine is misspelled to "glycine". Appropriate correction is required.

Rejection-35 U.S.C. 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Albert et al (WO 97/01579).

7. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog comprising the amino acid sequence of formula I.

8. Albert et al teach the somatostatin peptides, a process for their production and pharmaceutical preparations containing them (see p. 1, lines 1-3). The reference further teaches formula I –(D/L)Trp-Lys-X1-X2- and all variables (see pp. 1-2 and claim 1) that are associated with the formula I as instant claim 1. Furthermore, the reference teaches that the pharmaceutical composition comprising a somatostatin analog and pharmaceutically acceptable carriers or diluents therefor (see claims 8-9). This meets the limitation of claim 1.

9. Claims 1-3, 7-8 and 11-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Albert et al (WO 02/10192).

10. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog comprising the amino acid sequence

of formula I (in aspartate di-salt form) and II, and a pharmaceutical composition wherein the somatostatin analog is cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe]. Further, the claims are drawn to a method of preparation a pharmaceutical composition for the treatment of Cushing's disease.

11. Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable slat or complex thereof (see abstract). Additionally, the structural formula of instant claim 2 is shown in paragraph 2 and described in paragraph 3 as cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe] and is referred to as compound A (see paragraphs [0002], [0003], structure of formula on p. 1 and claim 1). This reads on claims 1 and 2. The reference further teaches that compound A or a pharmaceutically acceptable salt or complex thereof may be administered by any conventional route, for example parenterally (see p. 15, paragraph 4). This reads on claims 7-8, 11 and 12. Furthermore, the reference teaches that compound A may exist in free or salt form. Preferred salts are the lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt (see p. 3, paragraph 4). This reads on claims 3 and 12. Please note that claims 7-8 are treated as a method of making a medicament and no patentable weight was given to for treatment of Cushing's disease, as this describes and activity.

Rejection-35 U.S.C. 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-5 and 7-8 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (WO 02/10192) as applied to claims 1-3, 7-8 and 11-12 above, and further in view of Kamber B (US Patent # 4603120).

16. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog comprising the amino acid sequence of formula I and II, a pharmaceutical composition wherein the somatostatin analog is cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe], and a composition is adjusted to a pH of about 4 to about 4.5. Further, the claims are drawn to a method of preparation a pharmaceutical composition for the treatment of Cushing's Disease

17. As described above, Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable slat or complex thereof (see abstract). Additionally, the structural formula of instant claim 2 is shown in paragraph 2 and described in paragraph 3 as cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe] and is referred to as compound A (see paragraphs [0002], [0003], structure of formula on p. 1 and claim 1). This reads on claims 1 and 2. The reference further teaches that compound A or a pharmaceutically acceptable salt or complex thereof may be administered by any conventional route, for example parenterally (see p. 15, paragraph 4). This reads on claims 7-8, 11 and 12. Furthermore, the reference teaches that compound A may exist in free or salt form. Preferred salts are the lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt (see p. 3, paragraph 4). This reads on claims 3 and 12. Please note that claims 7-8 are treated as a method of

making a medicament and no patentable weight was given to for treatment of Cushing's disease. The differences between the reference and the instant claims are that the reference does not teach composition was adjusted to pH of 4 to 4.5.

18. However, Kamber B teach cyclopeptides of the somatostatin type and processes for their manufacture, and to pharmaceutical preparations containing these compounds and the use of these compounds or preparations for therapeutic purposes (see column 1, lines 7-11). Furthermore, the reference teaches the preparations may be used especially for parenterally administration (see column 15, lines 51-54). Furthermore, the reference teaches that preparations for parenteral administration in single-dose form...contain a buffer, for example a phosphate buffer, that is to maintain the pH between approximately 3.5 and 7, and also sodium chloride, mannitol or sorbotol for adjusting the isotonicity (see column 16, lines 1-9). This reads on claim 4.

19. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Albert et al and Kamber and adjusted the pH accordingly (optimize the pH), to maintain the pH between approximately 3.5 and 7 for parenteral administration because Kamber teaches that for parenteral administration the pH should be between 3.5 and 7 for somatostatin administration. The MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA*

1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); *In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a reasonable expectation of success to optimize the pH of the composition for parenteral administration, since pH of composition for parenteral administration is conventionally used between pH of 3.5 to 7. Additionally, "*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"

20. Claims 1-3, 7-8 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (WO 02/10192) in view of Stalla et al (European Journal of Endocrinology, 1994, 130: 125-131).

21. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog comprising the amino acid sequence of formula I and II, a pharmaceutical composition wherein the somatostatin analog is cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe]. Further, the claims are drawn to a method of preparation a pharmaceutical composition for the treatment of Cushing's Disease and a method of treating Cushing's Disease.

22. As described supra, Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable slat or complex thereof (see abstract). Additionally, the structural formula of instant claim 2 is shown in paragraph 2 and described in paragraph 3 as cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe] and is referred to as compound A (see paragraphs [0002], [0003], structure of formula on p. 1 and claim 1). This reads on claims 1 and 2. The reference further teaches that compound A or a pharmaceutically acceptable salt or complex thereof may be administered by any conventional route, for example parenterally (see p. 15, paragraph 4). This reads on claims 7-8, 11 and 12. Furthermore, the reference teaches that compound A may exist in free or salt form. Preferred salts are the lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt (see p. 3, paragraph 4). This reads on claims 3 and 12. Please note that claims 7-8 are treated as a method of

making a medicament and no patentable weight was given to for treatment of Cushing's disease. The difference between the reference and the instant claims is that the reference does not teach a method of treating Cushing's Disease.

23. However, Stalla et al teach that somatostatin analog octreotide (SMS 201-995) had different effects in vivo and in vitro in Cushing's disease (see Title). The reference teaches that octreotide could inhibit the ACTH release from human corticotropic adenoma cells in vitro but had no suppressive effect on ACTH levels of patients with Cushing's disease in vivo (see abstract). The reference teaches that octreotide suppressed ACTH serum levels in patients with adrenal insufficiency (Addison's disease) and in patients with Nelson's syndrome. This indicates that human corticotropic adenoma cells contain somatostatin receptors (see p. 125). The reference explains that since octreotide suppressed ACTH serum levels in both Addison's and Nelson's disease, the in vivo and in vitro discrepancy with Cushing's disease may be due to a somatostatin receptor down-regulation by cortisol at the hypercortisolemic state in vivo (see p. 125, 2nd paragraph). This reads on claims 13-14.

24. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Albert et al and Stalla et al to treat Cushing's disease. Albert et al teach somatostatin analogs and Stalla et al teach somatostatin analog in treating Cushing's Disease in vivo and in vitro, therefore, there is a reasonable expectation of success, since both teach somatostatin analog. And since Stalla et al teach treatment of Cushing's Disease, there is motivation of success, since both teach somatostatin analogs. Additionally, since Albert et al teach the compounds are useful for the

treatment of malignant cell proliferative diseases, e.g. cancer tumors, particularly tumors bearing the somatostatin receptor types targeted by the compounds (see p. 20, 3rd paragraph) and that corticotropic adenoma cells contain somatostatin receptors (see Stalla), it would have been obvious to use somatostatin analogs for treatment for Cushing's disease.

25. Claims 1 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (WO 02/10192) in view of Kamber B (US Patent # 4603120) as applied to claims 1-5, 7-8 and 11-14 above, and further in view of Bodmer et al (US Patent # 5639480).

26. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog wherein the composition is buffered by an acetate/acetic acid, lactate/lactic acid or glycine/HCl buffer.

27. As described supra, Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable slat or complex thereof (see abstract). Additionally, Kamber B teach cyclopeptides of the somatostatin type and processes for their manufacture, and to pharmaceutical preparations containing these compounds and the use of these compounds or preparations for therapeutic purposes (see column 1, lines 7-11). Furthermore, the reference teaches the preparations may be used especially for parenterally administration (see column 15, lines 51-54). Furthermore, the reference teaches that preparations for parenteral administration in single-dose form...contain a buffer, for example a phosphate buffer, that is to maintain the pH between

approximately 3.5 and 7, and also sodium chloride, mannitol or sorbotol for adjusting the isotonicity (see column 16, lines 1-9). The difference between the prior arts and the instant claims is that the reference does not teach the acetate buffer system.

28. However, the Bodmer et al teach microparticles comprising a somatostatin or an analog or derivative thereof (ocetretide) in a buffer system that may be prepared from acidic buffers such as phosphate buffer, acetate buffer and the like and the buffer may be from pH 2 to 8 with a pH 4 preferred (see abstract and column 9, lines 3-8). Further, the reference teaches that the microparticles can be administered in conventional manner, e.g. subcutaneous or intramusclular injection (see column 12, lines 6-7). This reads on claim 6.

29. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Albert et al, Kamber and Bodmer et al to administer the somatostatin in a buffer system containing acetate because for parenteral use, buffers such as phosphate and acetate can be used. There is a reasonable expectation of success, since all prior arts teach parenteral administration of somatostatin or analog thereof and Kamber teaches that parenteral administration in single-dose form contain a buffer, for example, a phosphate buffer, that is to maintain the pH between approximately 3.5 to 7 and Bodmer et al teach that emulsion may be buffered with a buffer which is non-detrimental to the peptide and the polymer matrix material (see column 9, lines 5-7). Thus, it would have been obvious to provide the composition in a buffer system to maintain the activity and inhibit the degradation of the somatostatin.

Conclusion

30. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1/22/07
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